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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,333	06/30/2003	Ramani R. Ranatunge	102258.153US	8773

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EXAMINER	
SOLOLA, TAOFIQ A	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,333	RANATUNGE ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *59-116* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *59-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 59-116 are pending in this application.

Claim 1-58 are cancelled.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.117(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/7/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification lacks adequate support for claims 59-116. According to the specification, compounds of formula II are nitrosated or nitrosylated derivatives of known COX-2 inhibitors. However, the specification fails to provide support for the compounds as meeting the general requirements of prodrugs. The specification states that the compounds may be nitrosated/nitrosylated through substituents such as oxygen, sulfur and/or nitrogen. However, there is no conclusive evidence that every compound of formula II has one or more of these

relevant substituents. One can only guess they do, even then one is not sure the exact position of the substituent(s). There are so many possible combinations in formula II, and it is not possible to ascertain the structures of compounds that are included and/or excluded by the claims.

There is no support for the claimed utilities in the specification by published journals or biological assays, and no support for using the compounds as combination therapy or cocktail. Only one species (example 1) is made and tested in the specification. The assay is limited to selective inhibition of COX-2 in whole blood. There is no relationship between the assay and the claimed utilities.

Prodrugs are generally designed to improve one or more of solubility, permeation, stability and pharmacokinetics. They are also used to direct a drug to a particular tissue or mask taste or odor. The specification discloses that nitrosated/nitrosylated derivatives of COX-2 inhibitors reduce gastrointestinal toxicity induced by non-nitrosated/nitrosylated COX-2 inhibitors. There is no assay to evidence this assertion, and none of the other requisites of a prodrug is disclosed in the specification for compounds of formula II. Nothing is disclosed in the specification to demonstrate how the instant compounds work in the body: are they metabolize to the known COX-2 inhibitors from which they are formed or not. If they are not, then applicant may not rely on the known non-nitrosated/nitrosylated COX-2 inhibitors to support the claimed utilities. If they do, the specification fails to show that compounds of formula II are not metabolized before getting to the point of action, that sufficient amount reaches the point of action, they are not toxic to the body in general, etc. The entire invention appears based on speculation since there is no conclusive evidence in the specification to support the claims.

The specification cited several patents, which are not incorporated by reference. However, these and other journals are not incorporated by reference in accordance with the MPEP, which states as follows:

A mere reference to another application, publication or patent is not an incorporation of anything therein into the application containing such reference for the purpose of satisfying the requirement of 35 USC 112, first paragraph. *In re de Seversky,* 474 F.2d 671, 177 USPQ 144 (CCPA 1973). Particular attention should be directed to the subject matter and the specific portions of the referenced document where the subject matter being incorporated may be found. MPEP 608.01(p).

If the document is a pending US application: prior to allowance of an application that incorporates essential material by reference to a pending US application, if the referenced application has not been published or issued as a patent, applicant is required to amend the disclosure of the referencing application to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating the amendment consists of the same material incorporated by reference in the referencing application. MPEP 608.01(p).

Claims 59-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using example 1 compound, for inhibiting COX-2, does not reasonably provide enablement for making and using all the nitrosated or nitrosylated compounds of formula II for treating all the claimed utilities or using the compounds in combination therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, It is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. at 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement."' *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed prodrugs, their combination and utility are not believable for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC, 1988):

"The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the

invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science.

For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. b) The direction concerning the instant prodrugs is not found in the specification. c) There is only one working example of a prodrug of compound II. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed.

Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.",

Marcel Dekker, New York, 1996, pages 451 and 596. In the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds, which may result from the combination of the numerous variables of formula II.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any compound of formula II has the required substituent: oxygen, sulfur and/or nitrogen for making nitrosated/nitrosylated derivatives, if in fact any of the derivatives meets the requirements of a prodrug, if the prodrugs are metabolized to the active drugs, if the prodrug in of itself is active, and if the active prodrug would treat any of the diseases listed in the claims. The purpose of 35 USC 112 is to obviate the need for this type of experimentation. *In re Borkowski,* 164 USPQ 642 (CCPA,1970). See also, *Univ. of Rochester v. G.D.Searle & Co,* 68 USPQ2d 1424 (DC WNY, 2003).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 59-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For reasons set forth above under 35 USC 112, first paragraph, the claims are indefinite.

Applicant's arguments filed 9/7/06 have been fully considered but they are not persuasive. Applicant contends that the utilities of COX-2 selective inhibitors are well known citing several prior arts in support thereof. This is not persuasive because as admitted by applicant, the instant compounds are prodrugs of selective COX-2 inhibitors. Applicant also argues that six species among the instant compounds are shown in the specification, citing table 1, page 120, to be selective COX-2 inhibitors. This is not persuasive because the examples are not commensurate in scope with the invention. While all the six examples are nitrooxy derivatives, the instant compounds are oxime, hydrazone and oxime-hydrazone derivatives. By limiting the compounds to the oxime derivatives wherein the oxime group is attached at position Y2 in formula II, the rejection would be overcome. This suggestion was agreed to by applicant in a recent telephone interview with the Examiner. Also, it was agreed that the method of use claims would be amended and he Examiner agreed to consider same. Yo 10/7/06

This is an RCE of applicant's earlier Application. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See

MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane, can be reached on (571) 272-0699. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

TAOFIQ SOLOLA
PRIMARY EXAMINER
Group 1626

October 7, 2006